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ORIGINAL ARTICLE

Age-related systemic treatment and survival of patients with metachronous metastases from colorectal cancer

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ABSTRACT

Background: Although the spectrum of systemic treatment for metastatic colorectal cancer (mCRC) has widened, there is a paucity of evidence for the feasibility and optimal use of these systemic agents in elderly patients. The present study provides real world data on the age-related systemic treatment and survival of CRC patients with non-resectable metachronous metastases.

Methods: All consecutive patients with non-resectable metastases from primary resected CRC were extracted from the Eindhoven area of the Netherlands Cancer Registry (NCR). Patients receiving palliative systemic therapy were enrolled (n = 385). Systemic treatment and survival were analyzed according to age at diagnosis of metastases.

Results: Patients aged ≥75 years more often received first-line single-agent chemotherapy than their younger counterparts (63% vs. 32%, $p < .0001$). First-line single-agent chemotherapy was often prescribed without additional targeted therapy (78%). Advanced age (≥75 years) was associated with a lower probability of receiving all active cytotoxic agents compared to patients aged <60 years at time of diagnosis of metastases (odds ratio (OR) 0.2, 95% CI 0.10–0.77). In a multivariable Cox regression analysis with adjustment for age and other relevant prognostic factors, the total number of received systemic agents was the only predictor of death (hazard ratio (HR) 0.7, 95% CI 0.61–0.81).

Conclusion: The beneficial effect of treatment with all active systemic agents on survival (simultaneously or sequentially prescribed) should be taken into account when considering systemic therapy in patients with mCRC. In light of our results, future studies are warranted to clarify the role of potential targeted therapy in elderly mCRC patients, who are often not candidates for combination chemotherapy and treatment with all active cytotoxic agents.

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Colorectal cancer (CRC) is the second most lethal cancer in the Netherlands. Most cancer-related deaths result from the progressive growth of metastases, which are present at time of diagnosis in approximately 20% of the patients [1–3] or occur during the course of disease in another 14–34% of the patients [4–8].

Since the late 1990s, the spectrum of systemic treatment in metastatic CRC (mCRC) has widened. Various systemic regimens combining fluoropyrimidines, oxaliplatin and irinotecan have become available, and more recently different monoclonal antibodies were introduced including bevacizumab, cetuximab and panitumumab.

The use of targeted therapy in addition to the available cytotoxic agents has been positively associated with survival [9,10]. The feasibility and optimal sequence of the administration of these systemic agents in elderly patients, however, is unclear. With the traditional under-representation of elderly patients in clinical trials [11], randomized data are scarce. High quality real-life studies are needed as the increasing proportion of elderly mCRC patients poses significant challenges to cancer specialists. The aim of the current study was to provide insight into the impact of age on the systemic treatment and survival of patients with unresectable metachronous metastases from CRC outside the setting of a randomized clinical trial.

Methods

Data collection

Data from the population-based Netherlands Cancer Registry (NCR), more specifically from the Eindhoven area, were used. This registry records data on all patients with newly diagnosed cancer in the southern part of the Netherlands, an area with approximately 2.4 million inhabitants (~15% of the Dutch population), six pathology departments, 10 hospitals

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and two radiotherapy institutions. Information on patient and tumor characteristics are collected from medical records by specially trained registry staff after notification by pathologists and medical registration offices, resulting in high quality of the data. In the NCR, primary tumors are classified according to the TNM classification of Malignant Tumors by the International Union Against Cancer (UICC), seventh edition [12]. Anatomical site of the tumor is registered according to the International Classification of Diseases for Oncology (ICD-O). A slightly modified version of the Charlson comorbidity index was used to register comorbidities.

For the present study, additional data were retrospectively collected between 2010 and 2011 on metachronous metastases for patients diagnosed between 2003 and 2008 with non-mCRC (stage I–III). Hospitals were asked to participate in the study by giving permission to use their data from the NCR and by giving permission for the retrospective registration of additional data. Metachronous metastases were defined as distant metastases of primary CRC in other organs, diagnosed at least three months after CRC diagnosis. Median time from primary diagnosis to data collection was 5.3 years (1.5–8.8 years). The additional data collection encompassed detailed information on systemic therapy, both chemotherapy and targeted therapy.

All consecutive patients with metachronous metastases from primary resected stage I–III CRC (C18.0–C18.9, C190, C209) were selected (n = 1007). Patients undergoing surgery for metastases (n = 261) or only supportive care (n = 361) were excluded for the present study, resulting in a study population of patients treated with palliative systemic therapy (n = 385). Patients were divided into categories according to their age at time of metachronous metastases diagnosis (<60 years, 60–75 years, ≥75 years) and palliative systemic treatment was assessed according to the number of received systemic agents and systemic treatment lines.

Statistical analyses

Descriptive statistics were used to provide an overview on patient and tumor characteristics of the total study population (n = 385). First-line systemic regimens were categorized according to the number of prescribed cytotoxic agents (single-agent chemotherapy, combination-chemotherapy) and the additional prescription of targeted therapy. Variation in the use of these systemic regimens between age categories was assessed using a χ^2-test. Duration of first-line treatment was calculated and presented as median duration in months. Differences in first-line duration between age categories were assessed and tested using a Wilcoxon rank sum test. Subsequently, proportions of patients receiving second-line systemic therapy were calculated and a multivariable logistic regression analysis was applied to investigate the independent influence of age on the receipt of second-line therapy. Adjustments were made for relevant patient and tumor characteristics: gender, comorbidity and socioeconomic status at time of CRC diagnosis, primary tumor localization, adjuvant chemotherapy, time to metastases, period of diagnosis of metastases, follow-up time since metastases diagnosis, the number of affected organs and the prescribed first-line regimen. This model was also applied to investigate the influence of age on the odds of exposure to all three active cytotoxic agents.

Overall survival (OS) time was defined as the time from diagnosis of the first metachronous metastatic site to death or lost to follow-up. Patients still alive at the end of follow-up (1 February 2016) and those who emigrated were censored. Crude survival estimates were calculated for both the total study population and according to age with the Kaplan-Meier method; crude survival rates were presented up to 48 months. A log-rank test was carried out to evaluate differences between survival curves. Median survival (MS) was presented in months and corresponding 95% confidence intervals (CIs). Multivariable Cox regression analyses were used to identify independent prognostic factors. Adjustments were made for clinically relevant variables that were applied in the multivariable logistic regression analysis, also including the total number of received systemic agents. p-Values below .05 were considered statistically significant. SAS/STAT® statistical software (SAS system 9.4, SAS Institute, Cary, NC) was used for all analyses.

Results

In total, 385 patients received palliative systemic therapy for the treatment of metachronous metastases from primary resected CRC. Mean age at time of metachronous metastases diagnosis was 67.5 years [standard deviation (SD) 10, range 26–90 years]. An overview of patient and tumor characteristics is shown in Table 1.

First-line systemic therapy

Table 2 provides an overview on the palliative systemic treatment of metachronous metastases from primary resected CRC. Of the total number of 385 patients, 60% received first-line combination chemotherapy (of which 94% oxaliplatin-based) and 40% received single-agent chemotherapy (of which 82% fluoropyrimidines). Targeted agents (mostly bevacizumab) were prescribed in 174 patients (45%), primarily in addition to combination chemotherapy. Significant differences in first-line systemic regimens were observed between age categories (Figure 1); elderly patients (≥75 years) more often received single-agent chemotherapy than their younger counterparts (63% ≥75 years vs. 27% <60 years).

Median duration of first-line treatment was 3.6 months [interquartile range (IQR) 1.3–8.4]. Significant differences in first-line treatment time were observed between age categories, with respectively 4.1 months (IQR 2.06–11.72) in patients <60 years, 3.6 months (IQR 1.57–8.37) in patients aged 60–75 years and 3.4 months (IQR 0.68–7.59) in patients aged ≥75 years.

Second and further lines of systemic treatment

Less than half of the patients (40%) received second-line therapy (n = 154, Figure 2a). With increasing age, the proportion

Table 1. Patient and tumor characteristics of the total study population of patients with metachronous metastases from primary resected stage I–III CRC treated with palliative systemic therapy (n = 385).

N = 385	N	(%)
Gender		
Male	154	(40)
Female	231	(60)
Age (years) at time of metastases diagnosis		
<60	83	(22)
60–75	202	(52)
≥75	100	(26)
Comorbidity at primary CRC diagnosis		
No	141	(37)
1 comorbid condition	112	(29)
≥2 comorbid conditions	104	(27)
Unknown	28	(7)
Socioeconomic status at primary CRC diagnosis		
Low	86	(22)
Intermediate	174	(45)
High	110	(29)
Institutionalized	7	(2)
Unknown	8	(2)
Primary tumor localization		
Rectum	160	(42)
Colon	225	(58)
Adjuvant chemotherapy		
No	226	(59)
Yes	159	(41)
Time to metastases (years)		
<1 year	247	(31)
1–2 years	255	(35)
≥2 years	244	(34)
Period of diagnosis of metastases		
2003–2005	77	(20)
2006–2008	197	(51)
2009–2011	111	(29)
Number of organs affected		
1 organ	168	(44)
2 organs	135	(35)
≥3 organs	82	(21)

CRC: colorectal cancer.

of patients receiving secondary treatment decreased, from 55% in patients <60 years to 26% in patients aged ≥75 years (p < .0001, Figure 2b). This was confirmed in a multivariable analysis in which patients aged ≥75 years at time of metachronous metastases diagnosis were less likely to receive second-line treatment than patients aged <60 years (odds ratio (OR) 0.3, 95% CI 0.16–0.80) (see Table 3).

Total number of received systemic agents during treatment course

–cytotoxic agents

Fluoropyrimidines were prescribed at any time during treatment course in 93% of the patients (mostly capecitabine), whereas oxaliplatin and irinotecan were prescribed in respectively 61% and 37%. A minority of the patients (22%) were exposed to all three cytotoxic agents (Table 2). Advanced age (≥75 years) was associated with a lower probability to receive all three active cytotoxic agents compared to patients aged <60 years at time of metastases diagnosis (OR 0.2, 95% CI 0.10–0.77, Table 3). Patients receiving first-line combination chemotherapy were more likely to receive

Table 2. Palliative systemic treatment of metachronous metastases from primary resected CRC, according to age at diagnosis of metastatic disease (n = 385).

	Total N = 385		<60 years N = 83		60–75 years N = 202		≥75 years N = 100		
	N	(%)	N	(%)	N	(%)	N	(%)	p-Value
First-line									
Single-agent CT_x	154	(40)	22	(27)	69	(34)	63	(63)	<.0001
+ targeted therapy	34	(22)	5	(23)	21	(30)	8	(13)	.04
− targeted therapy	120	(78)	17	(77)	48	(70)	55	(87)	
Combination CT_x	231	(60)	61	(73)	133	(66)	37	(37)	.45
+ targeted therapy	140	(61)	41	(67)	78	(59)	21	(57)	
− targeted therapy	91	(39)	20	(33)	55	(41)	16	(43)	
Total treatment									
Cytotoxic agents									
1	117	(30)	17	(21)	46	(23)	54	(54)	<.0001
2	184	(48)	36	(43)	111	(55)	37	(37)	
3	84	(22)	30	(36)	45	(22)	9	(9)	
Targeted agents									
0	169	(44)	27	(32)	79	(39)	63	(63)	<.001
1	190	(49)	48	(58)	107	(53)	35	(35)	
2	26	(7)	8	(10)	16	(8)	2	(2)	

CT_x: chemotherapy; cytotoxic agents: fluoropyrimidines (fluorouracil/capecitabine), oxaliplatin, irinotecan; targeted agents: anti-VEGF (bevacizumab), anti-EGFR (cetuximab/panitumumab).

all three cytotoxic agents than patients treated with first-line single-agent chemotherapy (OR 7.1, 95% CI 3.16–16.11).

–targeted agents

In total, 56% of the patients received additional targeted therapy during their course of disease (n = 216). Over time, the use of targeted therapy increased from 30% in 2003–2005 to 64% in 2009–2011. This trend was observed regardless of age, although in elderly patients (≥75 years) proportions increased primarily since 2009 whereas the increase in younger patients was observed already since 2005. Overall, proportions were significantly lower in patients aged ≥75 years (37%, Table 2).

Bevacizumab was the most frequently prescribed targeted agent (n = 207), which was added primarily to first-line systemic therapy (81%). Epidermal growth factor (EGFR) inhibitors (cetuximab/panitumumab) were administered to 35 patients (9%), mainly in addition to second-line treatment (n = 23).

Survival and predictors of death

Median OS of the total study population was 16.6 months (95% CI 14.42–19.19). Significant differences in OS time were observed between age categories, with respectively 14.2 months (95% CI 11.33–16.69) in patients ≥75 years and 20.3 months (95% CI 13.96–22.60) in patients <60 years (p < .01). After adjustment for relevant patient and tumor characteristics and treatment variables (first-line systemic therapy, number of exposed systemic agents) advanced age (≥75 years) was no longer significantly associated with OS (hazard ratio (HR) 1.3, 95% CI 0.90–1.86, p = .16). Although significant in univariate analysis (HR 0.7, 95% CI 0.57–0.86, p < .01), first-line combination chemotherapy also did not

Table 3. Predictors of treatment with second-line treatment and exposure to all three available cytotoxic agents, adjusted for all factors listed (n = 385).

	Second-line treatment				All three active cytotoxic drugs			
N = 385	(%)	OR	95% CI	p-Value	(%)	OR	95% CI	p-Value
Gender								
Male	(40)	Ref			(23)	Ref		
Female	(40)	0.9	0.54–1.44	.62	(21)	0.9	0.10–0.70	.84
Age (years) at time of metastases diagnosis								
<60	(55)	Ref			(36)	Ref		
60–75	(41)	0.6	0.32–1.09	.09	(22)	0.5	0.27–1.05	.42
≥75	(26)	**0.3**	**0.16–0.81**	**<.05**	(9)	**0.2**	**0.10–0.77**	**<.01**
Comorbidity at primary CRC diagnosis								
No	(46)	Ref			(26)	Ref		
1 comorbid condition	(36)	0.7	0.40–1.31	.28	(21)	0.9	0.46–1.81	.80
≥2 comorbid conditions	(34)	0.9	0.49–1.78	.83	(18)	1.2	0.56–2.58	.63
Unknown	(50)	1.0	0.38–2.61	.99	(21)	0.8	0.24–2.40	.64
Socioeconomic status at primary CRC diagnosis								
Low	(38)	1.2	0.65–2.49	.48	(20)	1.3	0.59–3.07	.46
Intermediate	(40)	1.0	0.63–1.89	.75	(24)	1.4	0.73–2.78	.29
High	(42)	Ref			(19)	Ref		
Institutionalized	(57)	2.4	0.39–14.98	.33	(29)	2.8	0.35–22.97	.32
Primary tumor localization								
Rectum	(46)	Ref			(27)	Ref		
Colon	(36)	0.8	0.46–1.24	.27	(18)	0.8	0.47–1.56	.62
Adjuvant chemotherapy								
No	(39)	Ref			(24)	Ref		
Yes	(42)	1.0	0.51–1.41	.90	(19)	0.8	0.47–1.56	.57
Time to metastases (years)								
<1 year	(40)	Ref			(25)	Ref		
1–2 years	(49)	1.5	0.85–2.80	.14	(29)	1.6	0.81–3.12	.18
≥2 years	(31)	1.0	0.49–1.83	.87	(12)	0.7	0.32–1.68	.47
Period of diagnosis of metastases								
2003–2005	(47)	Ref			(31)	Ref		
2006–2008	(46)	1.0	0.57–1.97	.84	(24)	0.6	0.34–1.37	.25
2009–2011	(25)	0.6	0.28–1.28	.18	(12)	0.4	0.16–1.09	.07
Number of organs affected								
1 organ	(38)	Ref			(23)	Ref		
2 organs	(39)	0.9	0.55–1.64	.85	(22)	0.7	0.38–1.36	.31
≥3 organs	(46)	1.2	0.67–2.36	.47	(21)	0.6	0.32–1.45	.32
First-line systemic therapy								
Single-agent chemotherapy	(33)	Ref			(5)	Ref		
Combination chemotherapy	(44)	1.0	0.64–1.82	.77	(33)	**7.1**	**3.16–16.11**	**<.0001**

CI: confidence interval; CRC: colorectal cancer also adjusted for follow-up time since metastases diagnosis. OR: odds ratio; Ref: reference. Bold indicate significant p-values.

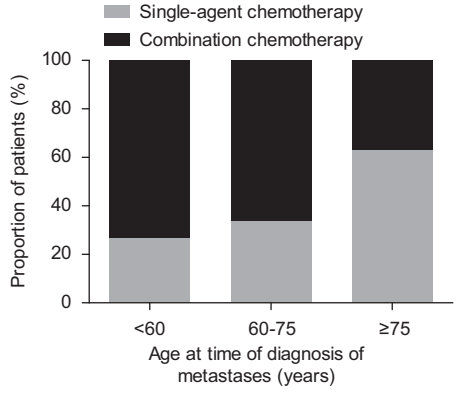

Figure 1. First-line chemotherapeutic regimens according to age at time of diagnosis of metachronous metastases (n = 385).

achieve significance in multivariate analysis (HR 1.2, 95% CI 0.86–1.56, p = .33), but the number of exposed systemic agents remained significantly associated with OS (HR 0.7, 95% CI 0.61–0.81, p < .0001).

Discussion

In the present population-based study we provided insight into the age-related systemic treatment and survival of patients with unresectable metachronous metastases from primary resected CRC.

We demonstrated that in everyday clinical practice only 26% of the elderly patients started second-line treatment. As most elderly patients received first-line single-agent chemotherapy without targeted therapy, elderly patients were less likely to receive all active systemic agents during their course of treatment, which was associated negatively with survival.

Overall, more than half (60%) of the mCRC patients received first-line combination chemotherapy with or without a targeted agent. As first-line treatment, combination chemotherapy has been associated with prolonged progression-free survival (PFS) and OS compared with single-agent chemotherapy [13–16]. Nevertheless, only a minority of the elderly patients (≥75 years) received combination chemotherapy (37%), probably due to concerns on tolerability and toxicity.

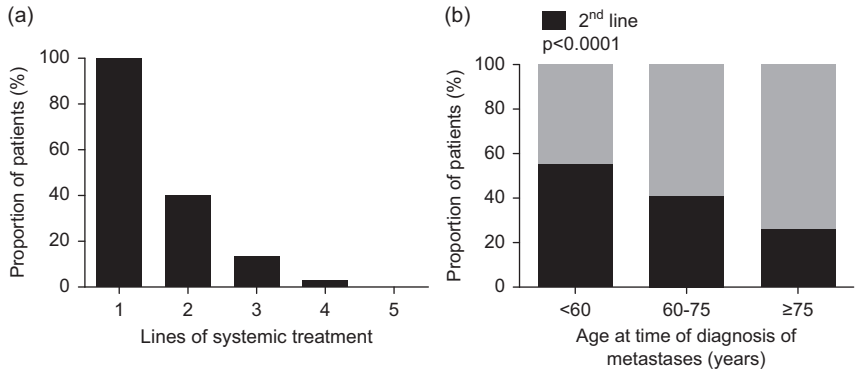

Figure 2. Proportion of patients receiving second and further lines of systemic treatment (a), according to age at time of diagnosis of metachronous metastases (b) (n = 385).

For a subgroup of patients with indolent disease, irrespective of age, there is no indication for combination chemotherapy. In the FOCUS2 trial investigating chemotherapy options in frail and elderly patients with advanced CRC, patients were randomly assigned to either intravenous fluorouracil with levofolinate, capecitabine, oxaliplatin and fluorouracil with levofolinate or oxaliplatin and capecitabine. Treatment was started at 80% of the standard dose as full dose regimens are often considered unsuitable in elderly and frail patients. The addition of oxaliplatin did not improve PFS [17]. Besides, the French FFCD2001-02 trial failed to demonstrate improved OS rates with irinotecan combination-chemotherapy versus single-agent fluorouracil with levofolinate although even greater toxicity rates were reported with irinotecan combination chemotherapy [18].

Regardless of the sequence of administration, exposure to all active cytotoxic agents during treatment has been associated with prolonged survival [19]. In view of this observation, it has been suggested that the sequential use of active single agents might be preferable to initial combination chemotherapy as this could conceivably reduce overall toxicity. Three European trials directly addressed this issue. In the FOCUS and FFCD 2000-05 trial, initial monotherapy followed by combination chemotherapy was non-inferior to initial combination therapy [20,21]. These results were endorsed by the CAIRO trial in which the sequential treatment strategy (first-line capecitabine, second-line irinotecan, third-line CAPOX) provided a similar benefit to initial combination treatment (first-line CAPIRI, second-line [22] CAPOX) [23].

The sequential treatment strategy, however, has several limitations. At first, it should not be initiated patients with potentially resectable metastases or severe cancer-related symptoms in whom the primary goal is downsizing of the tumor, as response rates are superior with combination chemotherapy [13,15]. Besides, sequential treatment implies that patients are still fit for second and further lines of treatment after progressing, which might not be the case in patients with an aggressive disease or a poor performance status. According to the study by Grothey et al., with data from seven phase III trials, 50–80% of the patients received second-line treatment after failure of first-line treatment [19]. In the present population-based study, higher dropouts rates were observed in everyday clinical practice (60% after first-line) due to the impact of a relatively large number of elderly patients. Only 26% of the elderly patients (≥75 years) received second-line therapy. This percentage is in line with the study by Sorbye et al., in which a poor performance status at start of first-line chemotherapy was identified as a poor predictor for administration of second-line treatment [24].

In our study, only 22% of the mCRC patients were exposed to all three cytotoxic drugs during their course of treatment. The likelihood of receiving all active cytotoxic agents was significantly lower with the use of first-line single-agent chemotherapy (5%) than with initial combination therapy (33%). These results are in line with data from the FOCUS and CAIRO trial, although proportions of patients receiving all cytotoxic agents in these two trials were higher. With the sequential treatment, 19% of the patients in the FOCUS trial and 36% of the patients in the CAIRO trial received all cytotoxic agents, whereas proportions were respectively 33% and 55% with initial combination treatment [21,23]. The dismal proportions as observed in our study probably arose from the relatively large proportion of elderly patients in daily based practice. In the present study, advanced age (≥75 years) was independently associated with a lower probability to access all three active cytotoxic drugs compared to patients aged <60 years.

During the current study period, elderly patients (≥75 years) were not only less likely to receive all active cytotoxic agents during their course of treatment, but also less frequently received targeted therapy. Initially, evidence on the use of bevacizumab – the first available and registered targeted agent in The Netherlands – was derived from a trial in which a currently outdated chemotherapy regimen (IFL) was used and elderly patients were under-represented [9]. Nowadays, several studies have suggested that bevacizumab is both safe and effective in combination with multiple chemotherapy backbone regimens [25], also in elderly patients [26–28] and that age itself should no longer be regarded an absolute contraindication. Probably as a result, bevacizumab was prescribed increasingly over time [22], also in elderly mCRC patients. Evidence on the use of other targeted agents such as anti-EGFR therapies (cetuximab, panitumumab) in elderly KRAS-wild type mCRC patients, however, remains scarce and less clear [29]. Recently, it has been suggested that single-agent panitumumab may be a well tolerated and active therapeutic option for frail elderly patients

with wild-type RAS tumors [30]. More studies are needed to clarify the role of anti-EGFR therapies in the population of elderly mCRC patients, especially as targeted agents may sometimes be the only therapeutic option for frail elderly patients who are unable to tolerate chemotherapy.

Several phase III trials [13–15,31,32] and retrospective cohort studies [22,33] have demonstrated survival rates exceeding 21.5 months in mCRC patients treated with modern systemic regimens, which seems in line with the median OS of 20.2 months in patients <60 years as observed in our study. Inferior results, however, were observed in elderly mCRC patients (≥75 years), with a median OS of 14 months. These results, along with results from a prior Nordic population-based registry [34], raise concerns over our ability to improve treatment options for elderly mCRC patients. In a multivariate analysis with adjustments for available prognostic factors, we found that only the number of exposed systemic agents was associated with OS, which suggests the need of a strategy to make all active agents available to patients with mCRC. Of course, these results need to be interpreted with caution due to the invariable presence of selection bias in this non-randomized study (patients who receive all drugs must live longer, since they need to be in shape for this), which cannot be fully out ruled in a multivariate analysis. Nevertheless, our results indicate that in elderly patients, initial treatment with the highest potential of improving both survival and maintaining quality of life is needed as most of these patients are not candidates for second-line treatment. Further studies are warranted to further define the role of targeted therapy in elderly mCRC patients who often are not candidates for intensive chemotherapy.

To the best of our knowledge, this is the first population-based study describing the whole spectrum of systemic treatment and survival of a long-term series of consecutive CRC patients with non-resectable metachronous metastases. The non-randomized nature of this study also presents a potential risk of (selection) bias. Reasons (not) to prescribe specific systemic regimens were not available. Besides, relevant patient characteristics such as comorbidity and performance score were registered only at initial CRC diagnosis. Moreover, performance score was often not noted in patient charts (missing in >50%) and as a result, these data were not useful. Data on RAS/BRAF mutation status were also not present. Despite these limitations, this large population-based study presents real world data which are of need in today's developing cancer care.

Conclusion

In daily practice, most elderly patients with non-resectable metachronous metastases from primary resected CRC receive first-line single-agent chemotherapy without a targeted therapy. Only a minority of the elderly mCRC patients receive a second line of treatment. As a consequence, very few elderly patients received all active systemic agents during their course of treatment, shown to be the only independent predictor of death. Future studies are needed to clarify the role of targeted therapy in elderly mCRC patients, who are often not candidates for combination chemotherapy.

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Disclosure statement

Both funders did not have any involvement in the study design, the collection, analysis and interpretation of data; in writing of the manuscript; and in the decision to submit the manuscript for publication.

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